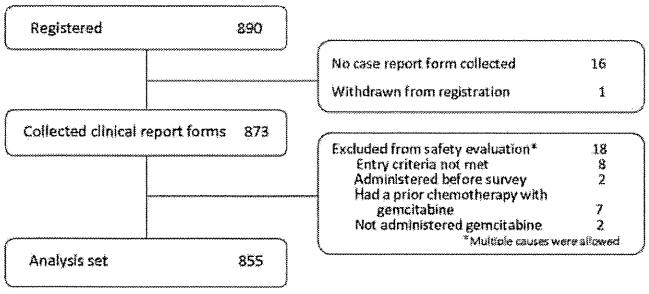

Figure 1. Patient disposition.

Table 1. Demographic and disease characteristics of patients

Characteristics		*n* (%)
Number of patients	All	855 (100.0)
Gender	Male	526 (61.5)
	Female	329 (38.5)
Age	<40	12 (1.4)
	40–49	46 (5.4)
	50–59	203 (23.8)
	60–69	338 (39.5)
	70–79	235 (27.5)
	80≤	21 (2.5)
Stage of disease in patients for primary pancreatic cancer ($n = 796$)	I	4 (0.5)
	II	18 (2.3)
	III	44 (5.5)
	IVa	222 (27.9)
	IVb	496 (62.3)
	Unknown	12 (1.5)
Performance status (PS)	0	302 (35.3)
	1	343 (40.1)
	2	101 (11.8)
	3	33 (3.9)
	4	6 (0.7)
	Unknown	70 (8.2)
Comorbidity	No	338 (39.5)
	Yes	517 (60.5)
	Hepatic function disorder[a]	210 (40.6)
	Renal function disorder[a]	17 (3.3)
	Blood disorder[a]	94 (18.2)
	Others[a]	402 (77.8)
Reason for gemcitabine usage	Primary pancreatic cancer	796 (93.1)
	Recurrent pancreatic cancer	55 (6.4)
	Others[b]	4 (0.5)
Histology of pancreatic cancer ($n = 851$[c])	Tubular adenocarcinoma	413 (48.3)
	Adenocarcinoma	63 (7.4)
	Papillary adenocarcinoma	24 (2.8)
	Adenosquamous carcinoma	6 (0.7)
	Acinar cell adenocarcinoma	5 (0.6)
	Others and unknown	340 (40.0)
Metastasis in primary pancreatic cancer ($n = 796$)	No	286 (35.9)
	Yes	499 (62.7)
	Unknown	11(1.4)
Primary chemotherapy	No	788 (92.2)
	Yes	67 (7.8)
Concomitant medication (anti-tumor drug)	No (monotherapy)	679 (79.4)
	Yes	176 (20.6)
Serum CA19-9 levels (U/ml) before first gemcitabine treatment ($n = 617$)	0≤ to ≤37	164 (26.6)
	37< to ≤100	66 (10.7)
	100< to ≤1000	174 (28.2)
	1000< to ≤10 000	134 (21.7)
	10000<	79 (12.8)

[a]Multiple answers allowed.
[b]Including one rectal cancer, two biliary carcinoma and one cholangiocellular carcinoma.
[c]Excluded four cases which had other cancer than PC.

Statistics

The percentage of patients who experienced ADRs was calculated.

The effectiveness analysis excluded the collected CRF of patients who were administered gemcitabine as a treatment for non-pancreatic cancers. Tumor response rate and disease control rate were evaluated based on all tumor response reported from attending physicians regardless of their day of assessment. Regarding DRSI, 'improvement' is defined as patients having at least one improvement with no aggravation in three symptoms (strength of pain, usage of analgesics and PS) and 7% weight gain. Time to treatment failure (TTF) was calculated for the days from the first administration to the 9th or last administration.

RESULTS

A total of 890 patients were registered by physicians and the CRFs of 873 patients were utilized for this surveillance (Fig. 1). Eighteen of the 873 patients were excluded, 855 patients from 125 institutions were evaluable for the safety analysis of gemcitabine. The types of PC and disease stages

Table 2. Dose administration for evaluable patients

Items	Results ($n = 855$)
Dosage (times)	
Median	9
Range	1–9
TTF[a] (days)	
Median	73
Range	1–295
Mean dosage (mg/m^2)	
Median	909.1
Range	10.0–1159.4
Total dosage (mg/m^2)	
Median	5960.3
Range	90.0–104 34.8

[a]Time to treatment failure.

were classified according to the sixth edition of *General Rules for the Study of Pancreatic Cancer* by Japan Pancreas Society.

Table 1 shows the characteristics of the 855 patients included in the safety analysis. Overall, patients were predominantly male (61.5%), ranging from 60 to 69 years of age (39.5%) and primarily in Stage IV (90.2%). About 75% of the patients had an ECOG PS of 0-1 and 11.8% had a PS of 2, suggesting that gemcitabine was mainly prescribed to favorable PS patients. For a majority of patients, gemcitabine was used as a first-line therapy, and tubular adenocarcinoma was the most common histology (48.3%). Of the 617 patients evaluated for serum CA19-9 levels for 14 days up to the first treatment, 174 of those (28.2%) were at the 100–1000 U/ml level and 134 (21.7%) at the 1000–10 000 U/ml level.

As shown in Table 2, 855 patients received gemcitabine a maximum of nine times over a median TTF of 73 days (range: 1–295 days). More than half of the patients received the full three cycles of gemcitabine. The median dose of gemcitabine per treatment was 909.1 mg/m^2 (range: 10.0–1159.4 mg/m^2) and the median amount of gemcitabine administered per patient was 5960.3 mg/m^2 (range: 90.0–104 34.8 mg/m^2).

In Table 3, ADRs with an incidence of $\geq$1% are summarized. Out of the total 855 evaluable patients, 444 patients (51.9%) experienced ADRs including 98 patients (11.5%) who experienced serious ADRs. Leukopenia and thrombocytopenia were the notable hematological toxicities and changes in the non-hematological parameters were rather insignificant. The maximum frequency of serious ADRs was 2.9% for leukopenia. Nausea and thrombocytopenia were also listed as ADRs with >1% incidence. Table 4 indicates the background information and outcome of ILD cases,

Table 3. Drug-related adverse events (incidence $\geq$1%)

Parameter	All, *n* (%)	Serious, *n* (%)
Evaluable patients	855 (100.0)	855 (100.0)
Patients with drug-related adverse events	444 (51.9)	98 (11.5)
Hematological toxicities		
Leukopenia	187 (21.9)	25 (2.9)
Thrombocytopenia	119 (13.9)	19 (2.2)
Neutropenia	52 (6.1)	6 (0.7)
Hemoglobin decreased	39 (4.6)	4 (0.5)
Anemia	38 (4.4)	2 (0.2)
Bone-marrow failure	36 (4.2)	8 (0.9)
Red-blood-cell count decreased	16 (1.9)	0 (0.0)
Hematocrit decreased	11 (1.3)	0 (0.0)
Non-hematological toxicities		
Nausea	63 (7.4)	11 (1.3)
Fever	40 (4.7)	7 (0.8)
Anorexia	40 (4.7)	7 (0.8)
Vomiting	28 (3.3)	5 (0.6)
Rash	27 (3.2)	2 (0.2)
Malaise	21 (2.5)	5 (0.6)
Hepatic dysfunction	20 (2.3)	3 (0.4)
Diarrhea	14 (1.6)	1 (0.1)
Hepatic disorder	11 (1.3)	0 (0.0)
Constipation	10 (1.2)	0 (0.0)
Rash, pruritic	9 (1.1)	0 (0.0)

which were reported from this study. All cases were over 60 years old. Sex, treatment line and tumor stage were reflected in the patient characteristics, and there was no correlation between treatment cycles, dosage or timing of ILD occurrence. Five of the six ILD cases recovered by using correct treatment, including steroid. There was one fatal case of a 69 years old male in poor performance status with stage IVa disease.

Table 5 showed the additional sub-group safety analysis. We examined the association between ADRs and patients characteristics, PS and age. The incidence of ADRs in PS $\geq$1 and PS 0 patients were 55.1 and 48.7%, respectively. The incidence of ADRs in patients $\leq$75 years old and >75 years old patients were 40.7 and 38.4%, respectively.

The tumor response of gemcitabine treatment was analyzed in 600 patients, taking complete response (CR), partial response (PR), minor response (MR), no change (NC) and progressive disease (PD) into consideration (Table 6). Although the overall response rate (CR+PR) was 6.0%, the disease control rate (CR + PR + MR + NC) was 54.0%. In order to evaluate the control of cancer-related symptoms, DRSI was also measured, as shown in Fig. 2. The number of patients responding was 185 (27.0%). Among four symptoms

Table 4. Background information and outcome of ILD cases in the study[a]

No.	Sex	Age	Line	Smoking history	Stage	PS (pre-treatment)	Gemcitabine treatment	Seriousness	Days from first dose to onset	Days from last dose to onset	Outcome	Days from onset to outcome
1	Male	68	Second	Unknown	IVb	1	10 00 mg/m^2 × 6 times	No	54	12	Recovering	15
2	Male	79	First	–	IVb	Unknown	1400 mg/body × 6 times	Yes	52	11	Recovered	10
3	Female	78	First	No	IVb	Unknown	1200 mg/body × 9 times	Yes	91	17	Recovering	9
4	Male	69	First	No	IVa	3	1000 mg/m^2 × 9 times	Yes	80	11	Death	34
5	Female	60	First	–	IVb	0	1400 mg/body × 1 time	Yes	25	25	Recovering	42
6	Male	68	First	Yes	IVb	2	1100 mg/body × 9 times + 800 mg/m^2 × 1 time[b]	Yes	91	21	Recovering	104

–, no data.
[a]Based on data reported by investigators.
[b]One dose was reported as post-treatment therapy.

Table 5. Sub-group safety analysis about the association between PS and age

Parameter	PS[a]				Age			
	PS0		≥PS1		≤75 years		>75 years	
	All, *n* (%)	Serious, *n* (%)	All, *n* (%)	Serious, *n* (%)	All, *n* (%)	Serious, *n* (%)	All, *n* (%)	Serious, *n* (%)
Evaluable patients	302		483		756		99	
Patients with drug-related adverse events	147 (48.7)	19 (6.3)	266 (55.1)	67 (13.9)	308 (40.7)	85 (11.2)	38 (38.4)	13 (13.1)
Hematological toxicities								
Leukopenia	60 (19.9)	6 (2.0)	117 (24.2)	16 (3.3)	164 (21.7)	21 (2.8)	23 (23.2)	4 (4.0)
Thrombocytopenia	30 (9.9)	0 (0.0)	86 (17.8)	17 (3.5)	107 (14.2)	18 (2.4)	12 (12.1)	1 (1.0)
Neutropenia	23 (7.6)	1 (0.3)	28 (5.8)	5 (1.0)	47 (6.2)	6 (0.8)	5 (5.1)	0 (0.0)
Hemoglobin decreased	11 (3.6)	1 (0.3)	28 (5.8)	3 (0.6)	36 (4.8)	3 (0.4)	3 (3.0)	1 (1.0)
Non-hematological toxicities								
Nausea	13 (4.3)	4 (1.3)	46 (9.5)	6 (1.2)	62 (8.2)	11 (1.5)	1 (1.0)	0 (0.0)
Fever	18 (6.0)	4 (1.3)	20 (4.1)	3 (0.6)	36 (4.8)	5 (0.7)	3 (3.0)	2 (2.0)
Anorexia	8 (2.6)	1 (0.3)	30 (6.2)	6 (1.2)	35 (4.6)	6 (0.8)	5 (5.1)	1 (1.0)
Vomiting	6 (2.0)	2 (0.7)	19 (3.9)	3 (0.6)	27 (3.6)	4 (0.5)	1 (1.0)	1 (1.0)
Hepatic dysfunction	3 (1.0)	0 (0.0)	7 (1.4)	0 (0.0)	8 (1.1)	0 (0.0)	3 (3.0)	0 (0.0)

[a]Seventy PS unknown cases were not included.

investigated, relief of pain was achieved most effectively, and even 4 weeks after the last administration, improvement of symptoms in response to gemcitabine therapy was observed in 19.6% of the patients.

Table 7 shows the changes in serum CA19-9 levels, revealing a decrease in 213 of the 335 patients (63.6%). CA19-9 decreased by ≥75% in 19.4% of the total group. According to additional analysis regarding the association between CA19-9 and tumor response, the overall response rate and disease control rate of patients whose CA19-9 had a ≥75% decrease were 21.5% (14/65) and 81.5% (53/65), respectively. The overall response rate and disease control rate of those whose CA19-9 levels had ≥50 to <75% decrease were 12.5% (6/48) and 60.4% (29/48), respectively.

DISCUSSION

This study is the first large-scale observational study to elucidate the safety profile of gemcitabine for Japanese PC patients. The results of this study indicated that the safety profiles of Japanese patients were consistent with the safety

profiles in previous reports of non-Japanese clinical studies (1). Incidence of serious bone-marrow suppression was <5% and gemcitabine appeared to be acceptable as a chemotherapeutic agent. Previous studies of anti-cancer drugs have indicated that drug-induced ILD is more commonly observed in Japan (5). The incidence of ILD associated with gemcitabine was 1.7% (36 patients in total out of 2110 enrollment) when investigated in non-small cell lung cancer patients in a Japanese post-marketing study (6). In this survey, ADRs occurred in 51.9% of the patients which was lower than that observed in the Japanese Phase I study (2). Because the study is post-marketing study as a non-interventional study, physical and laboratory examinations could not be stipulated but were just executed in clinical practice. And in this study, the data from laboratory examinations were not indispensable reporting items. In addition, the AEs in this large-scale study were evaluated by each attending physician. Thus, most commonplace AEs were not considered as significant to be recorded. The patients in clinical practice are less often and less intensively examined than ones in interventional clinical trials. That is why it should be noted that the study has a limitation when compared with other interventional clinical studies given difference in nature of studies.

Table 6. Anti-tumor effects of gemcitabine for pancreatic cancer patients in post-marketing surveillance

Parameter	Number of patients (%)
Analyzed patients	600 (100.0)
CR	6 (1.0)
PR	30 (5.0)
MR	14 (2.3)
NC	274 (45.7)
PD	276 (46.0)
NE	251
ORR (CR + PR)	36 (6.0)
DCR (CR + PR + MR + NC)	324 (54.0)

CR, complete response; PR, partial response; MR, minor response; NC, no change; PD, progressive disease; NE, not evaluable; ORR, overall response rate; DCR, disease-control rate.

According to additional analysis of the association between tumor response and CA19-9, tumor shrinkage was seen mainly in the patients whose CA19-9 level had decreased by more than 50%. This shows that there were more tumor controlled (CR, PR, MR or NC) patients whose CA19-9 level was ≥75% decrease rather than ≤50 to >75% decrease. Also, 21.3% of patients whose CA19-9 levels increased were observed to have tumor disease control (CR, PR, MR or NC). We experienced one 63 years old male patient whose CA19-9 level increased but showed tumor shrinkage. His CA19-9 level decreased after the end of his observational period. Therefore, we think that it is preferred to select the treatment option in reference to not only tumor marker evaluation but also tumor shrinkage in radiographic findings.

More than half of the patients successfully received gemcitabine treatment over nine times. Hence, gemcitabine appeared to be well tolerated by patients treated in daily clinical practice in Japan. An improvement in cancer-related symptoms after gemcitabine treatment was also observed. Its safety profile and tolerability was demonstrated in this study.

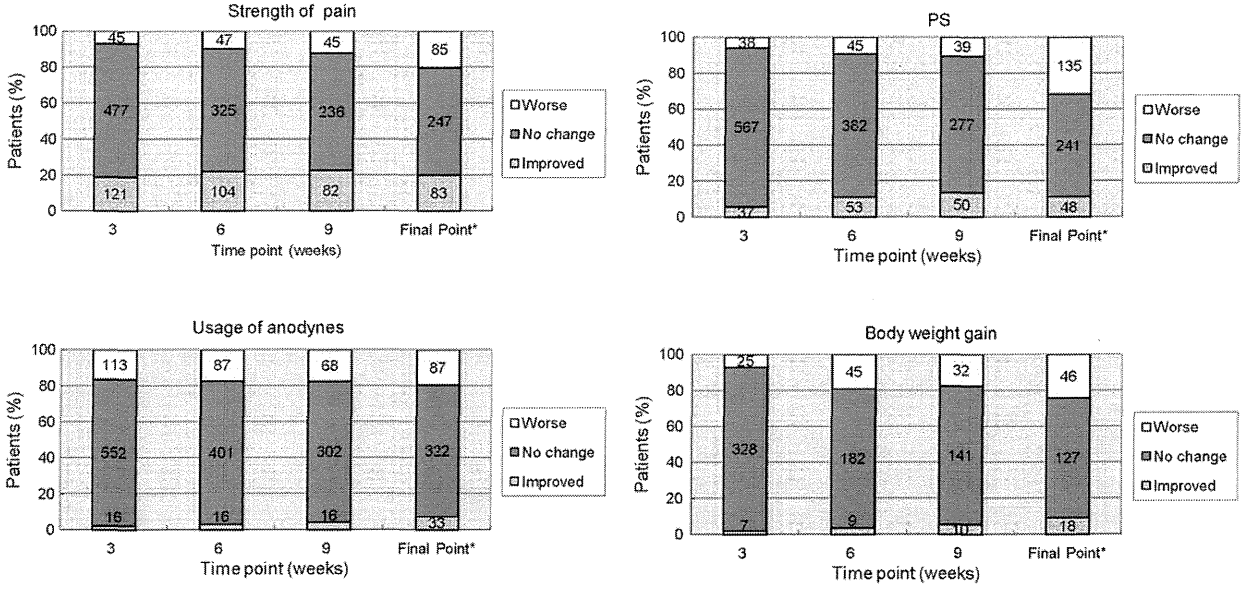

Figure 2. Disease-related symptom improvement in response to gemcitabine therapy. Total responders were 185/686 patients (27.0%): *4 weeks after the last administration.

Table 7. Change in serum CA19-9 levels in tumor response to gemcitabine therapy

Change in serum CA19-9	Number of patients (%)	ORR[a] (%)	DCR[b] (%)
Evaluable patients	335 (100.0)		
Decreased (total)	213 (63.6)	21/213 (9.9)	121/213 (56.8)
≥75% decreased	65 (19.4)	14/65 (21.5)	53/65 (81.5)
≥50 to <75% decreased	48 (14.3)	6/48 (12.5)	29/48 (60.4)
≥25 to <50% decreased	53 (15.8)	1/53 (1.9)	25/53 (47.2)
0–25% decreased	47 (14.0)	0/47 (0.0)	14/47 (29.8)
Increased (total)	122 (36.4)	1/122 (0.8)	26/122 (21.3)

[a](CR + PR)/(CR + PR + MR + NC + PD).
[b](CR + PR + MR + NC)/(CR + PR + MR + NC + PD).

In addition, its anti-tumor effects reinforce why gemcitabine treatment is currently considered to be one of the standards for advanced PC patients worldwide. In Japan, the effect of gemcitabine is demonstrated by a summary of the national PC registry in Japan, which indicated that the survival of PC patients has increased significantly since 2001; the authors of the study ascribe this improvement to the use of gemcitabine (7).

The 1-year survival rate of advanced PC patients treated with gemcitabine monotherapy is 18% (1) and there are many attempts to enhance the advanced pancreatic patient outcome by gemcitabine.

Given its mode of action (8), gemcitabine with a fixed-dosage rate, which may maximize the active intracellular form of gemcitabine, was examined in a large phase III study but failed to overcome standard regimen (9). Furthermore, a number of large phase III studies revealed gemcitabine monotherapy as the standard treatment for advanced PC (10). Some combination regimens with or without gemcitabine have shown promising survival benefits, including gemcitibine with erlotinib (11) and folfirinox (12). Considering vulnerability to toxic agents and poor PS of advanced PC patients in general, gemcitabine monotherapy remains a mainstay in clinical practice for treatment of advanced PC because of its good balance between efficacy and safety. With that in mind, a gemcitabine-based combination therapy, maintaining a good balance between efficacy and safety, can be anticipated.

In conclusion, this study with over 800 patients revealed that gemcitabine is well tolerated in Japanese PC patients. The study suggests clinical effectiveness in DRSI of gemcitabine even though there were some limitations due to the purpose and the framework of the study as a non-interventional study.

Acknowledgements

The authors acknowledge all physicians for their contribution to this research and Maki Ishikawa of Eli Lilly Japan K.K. and Donald Chow for their writing assistance.

Funding

This work was supported and funded by Eli Lilly Japan K.K.

Conflict of interest statement

H.T. and N.K. are employed by Eli Lilly Japan K.K.

References

1. Burris HA, III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–13.
2. Okada S, Ueno H, Okusaka T, Ikeda M, Furuse J, Maru Y. Phase I trial of gemcitabine in patients with advanced pancreatic cancer. *Jpn J Clin Oncol* 2001;31:7–12.
3. Guidelines to evaluate the response to treatment in solid tumors by Japan Society of Clinical Oncology. *Nihon Gan Chiryou Gakkai Shi* 1986;21:929–42.
4. Storniolo AM, Enas NH, Brown CA, Voi M, Rothenberg ML, Schilsky R. An investigational new drug treatment program for patients with gemcitabine: results for over 3000 patients with pancreatic carcinoma. *Cancer* 1999;85:1261–8.
5. Armour A. Gefitinib in advanced non-small cell lung cancer: clinical experience in patients of Asian origin. *Asia Pac J Clin Oncol* 2007;3:66–78.
6. Gemzar (gemcitabine) [Interview Form]: Eli Lilly Japan (In Japanese).
7. Egawa S. Summary of pancreatic or hepatic cancer patients with long term survival [Zenkoku shukei niyoru choki-seizon suikangan no jittai], Shokakigazo 2006.
8. Grunewald R, Abbruzzese JL, Tarassoff P, Plunkett W. Saturation of 2′,2′-difluorodeoxycytidine 5′-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. *Cancer Chemother Pharmacol* 1991;27:258–62.
9. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009;27:3778–85.
10. *NCCN Clinical Practice Guidelines in Oncology (NSSN Guidelines) Pancreatic Adenocarcinoma*, Version2. NCCN.org 2012. http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.
11. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007;25:1960–6.
12. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *New Engl J Med* 2011;364:1817–25.

Cancer Chemother Pharmacol (2012) 69:957–964
DOI 10.1007/s00280-011-1786-6

ORIGINAL ARTICLE

Phase I/II study of gemcitabine as a fixed dose rate infusion and S-1 combination therapy (FGS) in gemcitabine-refractory pancreatic cancer patients

Chigusa Morizane · Takuji Okusaka · Hideki Ueno · Shunsuke Kondo · Masafumi Ikeda · Junji Furuse · Ohkawa Shinichi · Kohei Nakachi · Shuichi Mitsunaga · Yasushi Kojima · Eiichiro Suzuki · Makoto Ueno · Tomohiro Yamaguchi

Received: 11 June 2011 / Accepted: 8 November 2011 / Published online: 26 November 2011

Abstract
Purpose There is no standard regimen for gemcitabine (Gem)-refractory pancreatic cancer (PC) patients. In a previous phase II trial, S-1 was found to exhibit marginal efficacy. Gem administration by fixed dose rate infusion of 10 mg/m^2/min (FDR-Gem) should maximize the rate of intracellular accumulation of gemcitabine triphosphate and might improve clinical efficacy. We conducted the phase I/II of FDR-Gem and S-1 (FGS) in patients with Gem-refractory PC.
Methods The patients received FDR-Gem on day 1 and S-1 orally twice daily on days 1–7. Cycles were repeated every 14 days. Patients were scheduled to receive Gem (mg/m^2/week) and S-1 (mg/m^2/day) at four dose levels in the phase I: 800/80 (level 1), 1,000/80 (level 2), 1,200/80 (level 3) and 1,200/100 (level 4). Forty patients were enrolled in the phase II study at recommended dose.
Results The recommended dose was the level 3. In the phase II, a partial response has been confirmed in seven patients (18%). The median overall survival time and median progression-free survival time are 7.0 and 2.8 months, respectively. The common adverse reactions were anorexia, leukocytopenia and neutropenia.
Conclusion This combination regimen of FGS is active and well tolerated in patients with Gem-refractory PC.

Keywords Chemotherapy · Pancreatic carcinoma · Second-line · Gemcitabine · S-1 · Salvage · Fixed dose rate infusion

Introduction

Gemcitabine monotherapy or gemcitabine-containing combination chemotherapy is the standard first-line therapy for advanced pancreatic cancer. In the recent phase III study, the first-line FOLFIRINOX regimen (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) led to a median survival of 11.1 months compared with 6.8 months in the gemcitabine group [4]. However, the FOLFIRINOX regimen was quite toxic (e.g., 5.4% of patients had grade 3 or 4 febrile neutropenia), and a survival benefit was shown only among a highly select population with a good performance status, an age of 75 years or younger, and normal or nearly normal bilirubin levels [13]. Therefore, this combination therapy was considered to be one of the treatment options for patients in good general condition, and gemcitabine remains the mainstay of care for patients with advanced pancreatic cancer. However, after disease progression during first-line gemcitabine-containing chemotherapy, the

The registration number of this clinical trial is UMIN ID, C000000450.

C. Morizane (✉) · T. Okusaka · H. Ueno · S. Kondo · T. Yamaguchi
Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: cmorizan@ncc.go.jp

M. Ikeda · K. Nakachi · S. Mitsunaga · Y. Kojima
Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, East, Kashiwa, Japan

J. Furuse · E. Suzuki
Division of Medical Oncology, Kyorin University School of Medicine, Tokyo, Japan

O. Shinichi · M. Ueno
Division of Hepatobiliary and Pancreatic Oncology, Kanagawa Cancer Center, Yokohama, Japan

options for further anticancer treatment are limited. S-1 is an orally administered anticancer drug that consists of a combination of tegafur, 5-chloro-2,4-dihydroxypyridine and oteracil potassium in a 1 : 0.4 : 1 molar ratio [27]. The antitumor effect of S-1 has already been demonstrated in a variety of solid tumors including pancreatic cancer [7, 11, 12, 14, 20, 21, 25, 26, 32, 33]. In patients with chemo-naïve pancreatic cancer, an overall response rate of 21.1% was achieved, and the median time-to-progression and median overall survival period were 3.7 and 8.3 months, respectively [32]. In gemcitabine-refractory metastatic pancreatic cancer, our recent phase II study of S-1 yielded results that demonstrated marginal activity including a response rate of 15%, a median progression-free survival time of 2.0 months and a median overall survival time of 4.5 months, with a favorable toxicity profile [17]. In addition, other reports also demonstrated marginal antitumor activity [1, 28]. Gemcitabine administration via infusion at a fixed dose rate of 10 mg/m^2/min (FDR-Gem) has been found to increase the intracellular drug concentrations, compared with gemcitabine at a standard dose rate infusion over a period of 30 min. A recent phase II study of combination therapy consisting of FDR-Gem and oxaliplatin (GEMOX) yielded results that demonstrated activity in gemcitabine-refractory advanced pancreatic cancer [5], although oxaliplatin is inactive against pancreatic cancer when used as a single agent [6]. The increased intracellular concentrations of gemcitabine as a result of FDR infusion and/or the synergistic effect of gemcitabine and oxaliplatin may play an important role in the antitumor effect of GEMOX. This finding is of interest when considering the effect of combination therapy consisting of FDR-Gem and some other agent that exhibits a synergistic effect with gemcitabine in patients with metastatic pancreatic cancer who failed standard dose rate gemcitabine.

The inhibition of ribonucleotide reductase by gemcitabine is considered to enhance the effect of the 5-FU metabolite 5-FdUMP by reducing the concentration of its physiological competitor [10]. Preclinical studies have demonstrated a synergy between gemcitabine and 5-FU in tumor cell lines, including pancreatic cancer cells [3, 23]. S-1 is a fluoropyrimidine, and several phase II studies of S-1 and gemcitabine combination therapy have yielded results that demonstrated a promising activity in chemo-naïve advanced pancreatic cancer patients, including a response rate of 32–48% and a median survival times of 7.89–12.5 months [16, 18, 19, 31].

Therefore, we conducted the present phase I/II study to determine the recommended doses of FDR-Gem and S-1 (FGS) to use for combination therapy and to evaluate the toxicity and efficacy at the recommended doses in patients with gemcitabine-refractory pancreatic cancer.

Materials and methods

Eligibility criteria

The eligibility criteria were histologically proven pancreatic adenocarcinoma with measurable metastatic lesions, disease progression during gemcitabine-based first-line chemotherapy, age 20 years or over, ECOG performance status of 0–2 points, more than 2-week interval between the final dose of the prior chemotherapy regimen and study entry, adequate bone marrow function (leukocyte count $\geq$ 3,500/mm^3, neutrophil count $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/mm^3, hemoglobin concentration $\geq$ 9.0 g/dL), adequate renal function (serum creatinine level $\leq$ 1.1 mg/dL) and adequate liver function (serum total bilirubin level $\leq$ 2.0 mg/dL, transaminase levels $\leq$ 100 U/L). Patients with obstructive jaundice or liver metastasis were considered eligible if their total bilirubin level $\leq$ 3.0 mg/dL and transaminase levels could be reduced to 150 U/L by biliary drainage. The exclusion criteria were regular use of phenytoin, warfarin or flucytosine, history of fluorinated pyrimidine use, severe mental disorder, active infection, ileus, watery diarrhea, interstitial pneumonitis or pulmonary fibrosis, refractory diabetes mellitus, heart failure, renal failure, active gastric or duodenal ulcer, massive pleural or abdominal effusion, brain metastasis, and active concomitant malignancy. Pregnant or lactating women were also excluded. Written informed consent was obtained from all patients. This study was approved by the institutional review board of the National Cancer Center of Japan.

Treatment

Considering the patients' quality of life, we adopted biweekly schedule. Gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) was administered by FDR intravenous infusion of 10 mg/m^2/min on day 1. S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) was administered orally twice daily on day 1 to day 7, followed by a 1-week rest. Treatment cycles were repeated every 2 weeks until disease progression or unacceptable toxicity occurred. If blood examination revealed leukocytopenia $<$ 2,000/mm^3, thrombocytopenia $<$ 75,000/mm^3, total bilirubin $>$ 3.0 mg/dL, aspartate aminotransferase or alanine aminotransferase level $>$ 150 U/L, or creatinine $>$ 1.5 mg/dL, both gemcitabine and S-1 were withheld until recovery. If a patient experienced dose-limiting toxicity (DLT), the dose of gemcitabine and S-1 was reduced by one level in the subsequent cycle. If a rest period of more than 15 days was required because of toxicity, the patient was withdrawn from the study. Patients were scheduled to receive gemcitabine and S-1 at four dosage levels (Table 1). Two dosage levels of S-1 were established according to the body

Table 1 Dosage levels of gemcitabine and S-1

Dosage level	Gemcitabine	S-1
Level 0	600 mg/m^2/60 min	Dosage A
Level 1[a]	800 mg/m^2/80 min	Dosage A
Level 2	1,000 mg/m^2/100 min	Dosage A
Level 3	1,200 mg/m^2/120 min	Dosage A
Level 4	1,200 mg/m^2/120 min	Dosage B

[a] Starting dosage

surface area as dosage A, about 80 mg/m^2/day, and dosage B, about 100 mg/m^2/day (Table 2). At the first dose level (level 1), gemcitabine was administered at a dosage of 800 mg/m^2 administered as a 80-min infusion, and S-1 was administered at dosage A. At the next dose level (level 2), the gemcitabine dosage was increased to 1,000 mg/m^2 administered as a 100-min infusion, and S-1 was administered at the same dosage. At the next dose level (level 3), the gemcitabine dosage was increased to 1,200 mg/m^2 administered as a 120-min infusion, and S-1 was administered at the same dosage. At the final dosage level (level 4), gemcitabine administered at the same dosage, and S-1 was administered at dosage B.

Study design

This study was an open-label, four-center, single-arm phase I/II study performed in two steps. The objective of step 1 (phase I) was to evaluate the frequency of DLT during first 2 cycles (4 weeks) and then use the frequency of DLT to determine which of the four dosages tested to recommend (Table 1). At least 3 patients were enrolled at each dosage level. If DLT was observed in the initial three patients, up to three additional patients were entered at the same dosage level. The highest dosage level that did not cause DLT in 3 of the 3 or $\geq$3 of the 6 patients treated at that level during the first two cycles of treatment was considered the maximum-tolerated dosage (MTD). DLT was defined as (1) grade 4 leucopenia or grade 4 neutropenia or febrile neutropenia, (2) grade 4 thrombocytopenia or thrombocytopenia requiring transfusion, (3) grade 3 or 4 non-hematological toxicity excluding hyperglycemia and electrolyte disturbances, (4) serum transaminases levels, γ-glutamyl transpeptidase level and alkaline phosphatase level $\geq$10 times UNL, (5) serum creatinine level $\geq$ 2.0 mg/dL and (6) any toxicity that necessitated a treatment delay of more than 15 days. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In step 2, the recommended dosages (RD) of FGS were then administered, and the effect of this combination therapy on objective tumor response was evaluated in patients who were given the RD (phase II). The number of patients to be enrolled in phase II was determined by using a SWOG's standard design (attained design) [8, 9]. The phase II included the patients who received the RD in the step 1. The null hypothesis was that the overall response rate would be $\leq$5%, and the alternative hypothesis was that the overall response rate would be $\geq$20%. The α error was 5% (one-tailed), and the β error was 10% (one-tailed). The alternative hypothesis was established based on the preferable data in previous reports [5, 15, 24, 30, 34]. Interim analysis was planned when 20 patients were enrolled. If none of the first 20 patients had a partial response or complete response, the study was to be ended. If a response was detected in any of the first 20 patients, an additional 20 patients were to be included in a second stage of accrual to more precisely estimate the actual response rate. If the number of objective responses after completing the trial was 5 or more among the 40 patients, then we would reject the null hypothesis and conclude that FGS was effective, and we would proceed to the next large-scale study. The severity of adverse events and progression-free survival and overall survival were investigated as secondary objectives in phase II.

Table 2 Dosage of S-1 (tegafur equivalent)

Body surface area (m^2)	Dosage A ($\fallingdotseq$80 mg/m^2/day)	Dosage B ($\fallingdotseq$100 mg/m^2/day)
<1.25	40 mg × 2/day	50 mg × 2/day
1.25–<1.5	50 mg × 2/day	60 mg × 2/day
$\geq$1.5	60 mg × 2/day	75 mg × 2/day

Results

Patient characteristics

Between June 2006 and March 2009, 49 patients were enrolled in this study. Fifteen patients (level 1: 3 patients, level 2: 3 patients, level 3: 6 patients, level 4: 3 patients) were enrolled into the phase I (STEP 1), and an additional 34 patients were enrolled into the phase II (STEP2) at dose level 3. Table 3 shows the baseline characteristics of the patients in step 1 and step 2. A total of the 40 patients who were given the recommended dose, 6 patients and 34 patients who entered into the study at phase I and phase II, respectively, were evaluated for efficacy and detailed safety profile.

Phase I (STEP 1)

No DLT occurred during the first 2 cycles (4 weeks) at level 1 or level 2. At dose level 3, three patients were

Table 3 Patient characteristics

Characteristic	Step 1				Step 2	Total at the recommended dose (level 3)
	Level 1	Level 2	Level 3	Level 4	Level 3	
No. of patients	3	3	6	3	34	40
Age, years						
Median	66	58	64	62	63.5	64
Range	55–69	51–58	48–71	52–70	40–80	40–80
Sex, *n* (%)						
Male	1 (33)	3 (100)	4 (67)	1 (33)	19 (56)	23 (58)
Female	2 (67)	0	2 (33)	2 (67)	15 (44)	17 (48)
ECOG performance status, *n* (%)						
0	2 (67)	2 (67)	5 (83)	2 (67)	22 (65)	27 (68)
1	1 (33)	1 (33)	1 (17)	1 (33)	12 (35)	13 (33)
Primary tumor, *n* (%)						
Head	1 (33)	2 (67)	2 (33)	2 (67)	17 (50)	19 (48)
Body/tail	2 (67)	1 (33)	4 (67)	1 (33)	17 (50)	21 (53)
Metastatic site, *n* (%)						
Liver	3 (100)	3 (100)	6 (100)	1 (33)	25 (74)	31 (78)
Lung	1 (33)	0	0	2 (67)	7 (21)	7 (18)
Peritoneum	1 (33)	1 (33)	0	1 (33)	11 (32)	11 (28)
Lymph node	0	2 (67)	0	0	11 (32)	11 (28)
Tumor stage at the start of prior treatment, *n* (%)						
Locally advanced	0	0	0	1 (33)	7 (21)	7 (18)
Metastatic	3 (100)	3 (100)	6 (100)	2 (67)	27 (79)	33 (83)
Prior treatment, *n* (%)						
Gemcitabine alone	3 (100)	3 (100)	5 (83)	3 (100)	26 (76)	31 (78)
Gem + Axitinib	0	0	0	0	2 (6)	2 (5)
Gem + Erlotinib	0	0	1 (17)	0	6 (18)	7 (18)

evaluated first, and none developed DLT. Since all 3 patients experienced DLT at dose level 4 (grade 4 neutropenia in two patients, grade 3 stomatitis in one patient), 3 additional patients were evaluated at dose level 3. A DLT (grade 4 neutropenia) was experienced by 2 of the 3 patients in this additional cohort in dose level 3, and dose level 3 was determined to be the MTD. Based on these results, the RD was determined to be level 3.

Phase II (efficacy and safety profile in the 40 patients treated at dose level 3)

In step 2, the RD of FDR-Gem and S-1 was administered to an additional 34 patients, and a total 40 patients were treated at dose level 3 to evaluate the objective tumor response to this combination therapy. As of the date of the analysis, the protocol treatment had been concluded in 39 of the 40 patients, and a total of 286 courses (median: 5 courses; range 1–31 courses) had been administered at level 3. The actual mean weekly dose administered were gemcitabine 545 mg/m^2/week (90.8% of planned dosage) and 90.1% of planned dosage of S-1. Dose reduction was required in 10 patients because of grade 4 neutropenia (five patients), grade 3 fatigue (1 patient), grade 2 fatigue with grade 2 appetite loss (one patient), grade 2 nausea (two patients) and grade 3 rash (1). The reasons for treatment discontinuation in phase II were radiological disease progression (33 patients), clinical disease progression (two patients), recurrent grade 4 neutropenia despite dose reduction due to grade 4 neutropenia (two patients), grade 4 myocardial infarction (one patients) and patient request to return to his distant hometown (one patient). All patients who discontinued treatment because of adverse events recovered from the toxicities after discontinuation. Twelve patients received third-line chemotherapy after discontinuation of FGS: S-1 monotherapy in four patients, gemcitabine + S-1 combination therapy on another treatment schedule in three patients, chemoradiotherapy with S-1 in one patient and new molecularly targeted agents in four patients who participated in a different clinical trial. Twenty-two patients received best supportive care, the other five patients transferred to another hospital, and no

information is available about their treatment after discontinuation of FGS.

Toxicity

All patients in steps 1 and 2 were evaluated for toxicity. In step 1, grade 3/4 non-hematological toxicity was observed in two patients (grade 3 fatigue during the third course in one patient, grade 3 stomatitis during the second course in one patient). No grade 4 leukocytopenia was observed at any dose level, but grade 4 neutropenia was observed in one out of three patients at dose level 1, none of the three patients at dose level 2, two of the six patients at dose level 3 and all three of the patients at dose level 4. Grade 3 thrombocytopenia was observed in one patient at dose level 2.

Table 4 summarizes the toxicities in the 40 patients who received the RD (level 3). All 40 eligible patients were assessable for toxicities, and FGS combination therapy at the RD was generally well tolerated. The most common toxicities were leukocytopenia (60%) and neutropenia (60%), but most of these toxicities were tolerable and reversible. Grade 4 neutropenia was noted as hematological toxicity in five patients (13%). Grade 3 non-hematological toxicities consisted of fatigue (one patient), vomiting (one patient), rash (one patient) and liver abscess (one patient). The patient who developed the grade 3 liver abscesses recovered after appropriate treatment with intravenous antibiotic alone. One female patient, who had hypercholesterolemia and history of smoking of 30 cigarettes/day, experienced a grade 4 acute myocardial infarction on day 1 of the third course of treatment, after gemcitabine had been administered but before the start of oral S-1. Emergency coronary angiography showed total occlusion of the left anterior descending coronary artery. The patient recovered from the cardiogenic shock due to myocardial infarction after coronary stent implantation and appropriate supportive treatment. S-1 monotherapy for the pancreatic cancer was started about 1 month after the infarction. No other severe or unexpected toxicities were noted in any of the patients.

Table 4 Treatment-related adverse events among the 40 patients who received the recommended dosages: highest grade reported during the treatment period

	Grade				Grade 1–4	Grade 3–4
	n					
	1	2	3	4	*n* (%)	*n* (%)
Hematological toxicities						
Leukocytes	11	4	9	0	24 (60)	9 (23)
Neutrophils	10	1	8	5	24 (60)	13 (33)
Hemoglobin	5	11	1	0	17 (43)	1 (3)
Platelets	11	2	1	0	14 (35)	1 (3)
Non-hematological toxicities					(0)	
Aspartate aminotransferase	8	1	0	0	9 (23)	0 (0)
Alanine aminotransferase	8	3	0	0	11 (28)	0 (0)
Alkaline phosphatase	5	2	0	0	7 (18)	0 (0)
Total bilirubin	3	0	0	0	3 (8)	0 (0)
Fatigue	15	2	1	0	18 (45)	1 (3)
Nausea	13	4	0	0	17 (43)	0 (0)
Vomiting	8	1	1	0	10 (25)	1 (3)
Anorexia	19	6	0	0	27 (68)	0 (0)
Stomatitis	4	0	0	0	4 (10)	0 (0)
Alopecia	8	0	–	–	8 (20)	–
Diarrhea	7	2	0	0	9 (23)	0 (0)
Rash	3	4	1	0	8 (20)	1 (3)
Hyperpigmentation	9	1	–	–	10 (25)	–
Hand-foot skin reaction	1	2	0	0	3 (8)	0 (0)
Watery eye	2	0	0	–	2 (5)	0 (0)
Hoarseness	1	0	0	0	1 (3)	0 (0)
Infection liver abscess	0	0	1	0	1 (3)	1 (3)
Myocardial infarction	0	0	0	1	1 (3)	1 (3)

Three patients died within 30 days after the final dose of the study drug. All 3 of the deaths were attributed to disease progression, and there were no treatment-related deaths.

Efficacy

It was possible to assess all 40 eligible patients who received the RD for response. Thirty-four patients had died by the completion of the follow-up period. There were no complete responses, but a partial response was achieved in seven patients (18, 95% confidence interval, 7.3–32.8%). Stable disease was noted in 19 patients (48%) and progressive disease in 14 patients (35%). Tumor responses to second-line FGS therapy are classified according to the tumor responses to first-line gemcitabine in Table 5. Three of 10 patients whose best response was progression disease in first-line chemotherapy achieved partial response in FGS therapy. The median progression-free survival time was 2.8 months. The median overall survival time after the start of second-line therapy was 7.0 months (range 1.3–18.9+), and the 1-year survival rate was 18% (Fig. 1). The median overall survival time after the start of first-line therapy was 13.9 months (range 5.2–31.4).

Table 5 Objective tumor response

Response (2nd line)	*n* (%)	Response (1st line)		
		PR	SD	PD
PR	7 (18)	1	3	3
SD	19 (48)	3	12	4
PD	14 (35)	2	9	3
Total	40 (100)	6	24	10

Response rate: 18% (95% CI: 7.3–32.8)

RECIST criteria

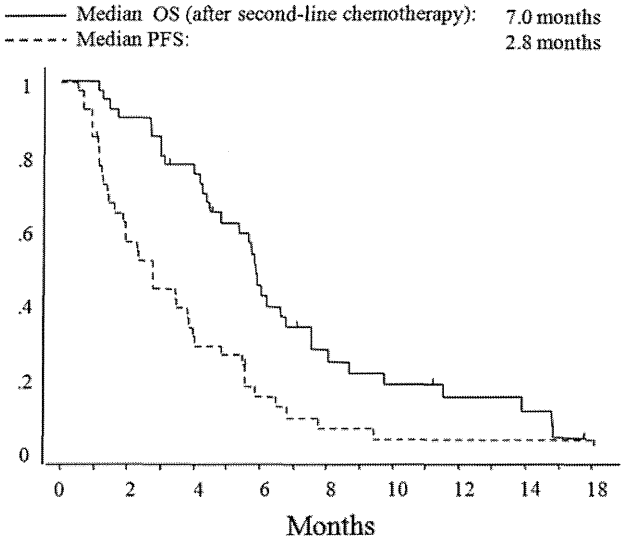

Fig. 1 Survival curves. Survival ($n = 40$). Progression-free survival (*dashed line*) and overall survival time (*solid line*) curves of patients with gemcitabine-refractory pancreatic cancer receiving systemic chemotherapy with FGS

Discussion

In the last decade, several clinical trials (mainly phase II) have been conducted in patients with advanced pancreatic cancer after failure of first-line gemcitabine or a gemcitabine-based combination regimen. The results of a randomized trial ($n = 168$) comparing fluorouracil and folinic acid versus oxaliplatin, fluorouracil and folinic acid (OFF) indicated that OFF improved progression-free survival and overall survival as a second-line chemotherapy. The median progression-free survival time and median survival time of OFF were 3 and 6 months, respectively [22]. In the present study, FGS yielded a median progression-free survival time of 2.8 months and a median overall survival time of 7.0 months, similar to the data mentioned above. Furthermore, the response rate of 18% in the present study was above the pre-established boundary (objective response in five or more of the 40 patients) required for the regimen to be considered effective. However, the gap between the median overall survival time and the median progression-free survival time in the present study was relatively large. Although the reason for this gap is unknown, a bias arising from the selection of patients with a good general condition or with a small tumor burden may explain these findings.

Whether gemcitabine as an FDR infusion is active even after progression during treatment with the standard 30-min administration of gemcitabine was the critical clinical question examined in this study. Differentiating between the relative roles of gemcitabine and S-1 in overcoming tumor resistance is difficult. The efficacy and survival data obtained in the present study seem to be better than those of previous studies for oral fluoropyrimidine monotherapy as a salvage chemotherapy for advanced pancreatic carcinoma (Table 6) [1, 2, 17, 28, 29]. However, since all the data were obtained in single-arm studies, a randomized study is needed to make these suggestions reliable. Furthermore, whether the combined regimen in the present study is superior to other regimens, such as the OFF regimen, remains an essential clinical question.

Safety and convenience as well as antitumor efficacy are critically important issues with regard to second-line chemotherapy. One patient experienced an acute myocardial infarction. Although she had other risk factors, such as a smoking habit and hyperlipidemia, a relation between gemcitabine and the acute myocardial infarction cannot be ruled out because gemcitabine had been administered on the day of the infarction. The toxicity profile of FGS

Table 6 Comparison between the current study and previous studies of oral fluoropyrimidine monotherapy as salvage chemotherapy for advanced pancreatic carcinoma

Study	References	Phase	Regimen	*n*	PR + CR (%)	Median PFS (months)	Median OS (months)
Morizane et al.	[12]	II	S-1	40	15	2.0	4.5
Abbruzzese et al.	[29]	II	S-1	45	0	1.4	3.1
Sudo et al.	[31]	II	S-1	21	9.5	4.1	6.3
Todaka et al.	[32]	Retrospective	S-1	52	4	2.1	5.8
Boeck et al.	[30]	II	Capecitabine	39	0	2.3	7.6
Morizane et al.	Current study	II	FGS	40	18	2.8	7.0

therapy in the other patients was acceptable, and the most common grade 1–4 adverse reactions were anorexia (68%), leukocytopenia (60%) and neutropenia (60%), although most episodes were tolerable and reversible. The safety profile in this study suggests that FGS can be safely administered to pancreatic cancer patients even in a second-line setting, at least in select populations. The biweekly schedule allows enough time to recover from myelosuppression and non-hematological toxicities before the following cycle, enabling patients to receive treatment as scheduled. Actually, the relative dose intensities of gemcitabine and S-1 in our study were high (90.8 and 90.1%, respectively). Furthermore, because of the biweekly schedule, patients do not need to come to the hospital for treatment as often compared with the first-line standard schedule of gemcitabine therapy. Our new treatment schedule may therefore improve the patients' quality of life during anticancer treatment.

We concluded that combination therapy consisting of gemcitabine as a fixed dose rate infusion and S-1 (FGS) provided a promising antitumor activity and tolerable toxicity in patients with gemcitabine-refractory metastatic pancreatic cancer. A larger randomized controlled trial is needed to confirm the clinical benefits of FGS following gemcitabine failure.

References

1. Abbruzzese JL, Lenz H, Hanna W, Kindler HL, Scullin D, Nemunaitis J, Kudva G, Zhang J, Zergebel C, Urrea P (2009) Open-label phase II study of S-1 as second-line therapy for patients with metastatic pancreatic cancer. 2009 Gastrointestinal Cancers Symposium Abstract No: 243
2. Boeck S, Wilkowski R, Bruns CJ, Issels RD, Schulz C, Moosmann N, Laessig D, Haas M, Golf A, Heinemann V (2007) Oral capecitabine in gemcitabine-pretreated patients with advanced pancreatic cancer. Oncology 73:221–227
3. Bruckner HW, Zhou G, Haenel P, Szraijer L, Greenspan E, Kurbacher CM (1998) Ex vivo ATP tumor testing of gemcitabine for combination chemotherapy and biochemical modulation. Proc Am Assoc Cancer Res 39
4. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiere C, Bennouna J, Bachet JB, Khemissa-Akouz F, Pere-Verge D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825
5. Demols A, Peeters M, Polus M, Marechal R, Gay F, Monsaert E, Hendlisz A, Van Laethem JL (2006) Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. Br J Cancer 94:481–485
6. Ducreux M, Mitry E, Ould-Kaci M, Boige V, Seitz JF, Bugat R, Breau JL, Bouche O, Etienne PL, Tigaud JM, Morvan F, Cvitkovic E, Rougier P (2004) Randomized phase II study evaluating oxaliplatin alone, oxaliplatin combined with infusional 5-FU, and infusional 5-FU alone in advanced pancreatic carcinoma patients. Ann Oncol 15:467–473
7. Furuse J, Okusaka T, Boku N, Ohkawa S, Sawaki A, Masumoto T, Funakoshi A (2008) S-1 monotherapy as first-line treatment in patients with advanced biliary tract cancer: a multicenter phase II study. Cancer Chemother Pharmacol 62:849–855
8. Green SJ, Benedetti J, Crowley J (1997) Clinical trials in oncology, 2nd edn. Chapman and Hall/CRC, London, pp 53–58
9. Green SJ, Dahlberg S (1992) Planned versus attained design in phase II clinical trials. Stat Med 11:853–862
10. Heinemann V, Xu YZ, Chubb S, Sen A, Hertel LW, Grindey GB, Plunkett W (1990) Inhibition of ribonucleotide reduction in CCRF-CEM cells by 2', 2'-difluorodeoxycytidine. Mol Pharmacol 38:567–572
11. Inuyama Y, Kida A, Tsukuda M, Kohno N, Satake B (2001) Late phase II study of S-1 in patients with advanced head and neck cancer. Gan To Kagaku Ryoho 28:1381–1390
12. Kawahara M, Furuse K, Segawa Y, Yoshimori K, Matsui K, Kudoh S, Hasegawa K, Niitani H (2001) Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. Br J Cancer 85:939–943
13. Kim R (2011) FOLFIRINOX: a new standard treatment for advanced pancreatic cancer? Lancet Oncol 12:8–9
14. Koizumi W, Kurihara M, Nakano S, Hasegawa K (2000) Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 cooperative gastric cancer study group. Oncology 58:191–197
15. Kozuch P, Grossbard ML, Barzdins A, Araneo M, Robin A, Frager D, Homel P, Marino J, DeGregorio P, Bruckner HW (2001) Irinotecan combined with gemcitabine, 5-fluorouracil, leucovorin, and cisplatin (G-FLIP) is an effective and noncross-resistant treatment for chemotherapy refractory metastatic pancreatic cancer. Oncologist 6:488–495
16. Lee GW, Kim HJ, Ju JH, Kim SH, Kim HG, Kim TH, Jeong CY, Kang JH (2009) Phase II trial of S-1 in combination with gemcitabine for chemo-naive patients with locally advanced or

metastatic pancreatic cancer. Cancer Chemother Pharmacol 64:707–713
17. Morizane C, Okusaka T, Furuse J, Ishii H, Ueno H, Ikeda M, Nakachi K, Najima M, Ogura T, Suzuki E (2009) A phase II study of S-1 in gemcitabine-refractory metastatic pancreatic cancer. Cancer Chemother Pharmacol 63:313–319
18. Nakamura K, Yamaguchi T, Ishihara T, Sudo K, Kato H, Saisho H (2006) Phase II trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. Br J Cancer 94:1575–1579
19. Oh DY, Cha Y, Choi IS, Yoon SY, Choi IK, Kim JH, Oh SC, Kim CD, Kim JS, Bang YJ, Kim YH (2010) A multicenter phase II study of gemcitabine and S-1 combination chemotherapy in patients with unresectable pancreatic cancer. Cancer Chemother Pharmacol 65:527–536
20. Ohtsu A, Baba H, Sakata Y, Mitachi Y, Horikoshi N, Sugimachi K, Taguchi T (2000) Phase II study of S-1, a novel oral fluorophyrimidine derivative, in patients with metastatic colorectal carcinoma. S-1 cooperative colorectal carcinoma study group. Br J Cancer 83:141–145
21. Okusaka T, Funakoshi A, Furuse J, Boku N, Yamao K, Ohkawa S, Saito H (2008) A late phase II study of S-1 for metastatic pancreatic cancer. Cancer Chemother Pharmacol 61:615–621
22. Pelzer U, Kubica K, Stieler J, Schwaner I, Heil G, Görner M, Mölle M, Hilbig A, Dörken B, Riess H, Oettle H (2008) A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study. J Clin Oncol 26(15S) (May 20 Supplement), ASCO Annual Meeting Proceedings (Post-Meeting Edition)
23. Ren Q, Kao V, Grem JL (1998) Cytotoxicity and DNA fragmentation associated with sequential gemcitabine and 5-fluoro-2'-deoxyuridine in HT-29 colon cancer cells. Clin Cancer Res 4:2811–2818
24. Reni M, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, Luppi G, Nicoletti R, Galli L, Bordonaro R, Passardi A, Zerbi A, Balzano G, Aldrighetti L, Staudacher C, Villa E, Di Carlo V (2005) Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. Lancet Oncol 6:369–376
25. Saek T, Takashima S, Sano M, Horikoshi N, Miura S, Shimizu S, Morimoto K, Kimura M, Aoyama H, Ota J, Noguchi S, Taguchi T (2004) A phase II study of S-1 in patients with metastatic breast cancer–a Japanese trial by the S-1 cooperative study group, breast cancer working group. Breast Cancer 11:194–202
26. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T (1998) Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 34:1715–1720
27. Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, Fukushima M (1996) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 7:548–557
28. Sudo K, Yamaguchi T, Nakamura K, Denda T, Hara T, Ishihara T, Yokosuka O (2011) Phase II study of S-1 in patients with gemcitabine-resistant advanced pancreatic cancer. Cancer Chemother Pharmacol 67:249–254
29. Todaka A, Fukutomi A, Boku N, Onozawa Y, Hironaka S, Yasui H, Yamazaki K, Taku K, Machida N, Sakamoto T, Tomita H (2010) S-1 monotherapy as second-line treatment for advanced pancreatic cancer after gemcitabine failure. Jpn J Clin Oncol 40:567–572
30. Tsavaris N, Kosmas C, Skopelitis H, Gouveris P, Kopterides P, Loukeris D, Sigala F, Zorbala-Sypsa A, Felekouras E, Papalambros E (2005) Second-line treatment with oxaliplatin, leucovorin and 5-fluorouracil in gemcitabine-pretreated advanced pancreatic cancer: a phase II study. Invest New Drugs 23:369–375
31. Ueno H, Okusaka T, Furuse J, Yamao K, Funakoshi A, Boku N, Ohkawa S, Yokosuka O, Tanaka K, Moriyasu F, Nakamori S, Sato T (2011) Multicenter phase II study of gemcitabine and S-1 combination therapy (GS Therapy) in patients with metastatic pancreatic cancer. Jpn J Clin Oncol 41:953–958
32. Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C (2004) Phase II study of S-1 in patients with advanced biliary tract cancer. Br J Cancer 91:1769–1774
33. Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C (2005) An early phase II study of S-1 in patients with metastatic pancreatic cancer. Oncology 68:171–178
34. Ulrich-Pur H, Raderer M, Verena Kornek G, Schull B, Schmid K, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Scheithauer W (2003) Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. Br J Cancer 88:1180–1184

Cancer Chemother Pharmacol (2012) 69:1197–1204
DOI 10.1007/s00280-012-1822-1

ORIGINAL ARTICLE

Randomized phase II study of gemcitabine and S-1 combination versus gemcitabine alone in the treatment of unresectable advanced pancreatic cancer (Japan Clinical Cancer Research Organization PC-01 study)

Masato Ozaka · Yuji Matsumura · Hiroshi Ishii · Yasushi Omuro · Takao Itoi · Hisatsugu Mouri · Keiji Hanada · Yasutoshi Kimura · Iruru Maetani · Yoshinobu Okabe · Masaji Tani · Takaaki Ikeda · Susumu Hijioka · Ryouhei Watanabe · Shinya Ohoka · Yuki Hirose · Masafumi Suyama · Naoto Egawa · Atsushi Sofuni · Takaaki Ikari · Toshifusa Nakajima

Received: 23 November 2011 / Accepted: 31 December 2011 / Published online: 17 January 2012

Abstract
Purpose To evaluate the efficacy and safety of the combination of gemcitabine (GEM) and S-1 (GS) in comparison to GEM alone (G) for unresectable pancreatic cancer.
Methods In this multicenter randomized phase II study, we randomly assigned unresectable pancreatic cancer patients to either the GS group or the G group. The GS group regimen consists of intravenous 1,000 mg/m^2 GEM during 30 min on days 1 and 8, combined with 80 mg/m^2 oral S-1 twice daily on days 1–14, repeated every 3 weeks. On the other hand, the G group regimen consists of intravenous 1,000 mg/m^2 GEM on days 1, 8, and 15, repeated every 4 weeks. The primary endpoint was objective response rate (ORR). Secondary end points included treatment toxicity, clinical response benefit, progression-free survival (PFS), and overall survival.

M. Ozaka (✉) · H. Ishii
Department of Gastroenterology, Cancer Institute Hospital, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan
e-mail: masato.ozaka@jfcr.or.jp

Y. Matsumura · M. Suyama
Department of Gastroenterology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

Y. Omuro
Department of Chemotherapy, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan

T. Itoi · A. Sofuni
Department of Gastroenterology and Hepatology, Tokyo Medical University Hospital, 6-7-1, Nishi-Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

H. Mouri
Cancer Center, Kanazawa University, 13-1, Takara-machi, Kanazawa, Ishikawa 920-0934, Japan

K. Hanada
Department of Gastroenterology, JA Onomichi General Hospital, 1-10-23 Hirahara, Onomichi, Hiroshima 722-8508, Japan

Y. Kimura
Department of Surgical Oncology and Gastroenterological Surgery, Sapporo Medical University School of Medicine, South-1, West-16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan

Y. Kimura
Department of Surgical Oncology and Gastroenterological Surgery, Sapporo Medical University School of Medicine, South-1, West-16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan

I. Maetani
Division of Gastroenterology, Department of Internal Medicine, Toho University Ohashi Medical Center, 2-17-6 Ohashi, Meguro, Tokyo 153-8515, Japan

Y. Okabe
Division of Gastroenterology, Department of Medicine, School of Medicine, Kurume University, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan

M. Tani
Second Department of Surgery, School of Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-8510, Japan

T. Ikeda
Department of Gastroenterology, Yokosuka Kyosai Hospital, 1-16 Yonegahamadori, Yokosuka, Kanagawa 238-8558, Japan

S. Hijioka
Department of Gastroenterology, Kumamoto Red Cross Hospital, 2-1-1, Nagamine-minami, Kumamoto 861-8520, Japan

R. Watanabe
Department of Surgery, Matsuyama Shimin Hospital,

Results We registered 117 patients from 16 institutions between June 2007 and August, 2010. The ORR of the GS group was 28.3%, whereas that of the G group was 6.8%. This difference was statistically significant ($P = 0.005$). The disease control rate was 64.2% in the GS group and 44.1% in the G group. Median PFS was 6.15 months in the GS group and 3.78 month in the G group. This was also statistically significant ($P = 0.0007$). Moreover, the median overall survival (OS) of the GS group was significantly longer than that of the G group (13.7 months vs. 8.0 months; $P = 0.035$). The major grade 3–4 adverse events were neutropenia (54.7% in the GS group and 22.0% in the G group), thrombocytopenia (15.1% in the GS group and 5.1% in the G group), and skin rash (9.4% in the GS group).
Conclusions The GS group showed stronger anticancer activity than the G group, suggesting the need for a large randomized phase III study to confirm GS advantages in a specific subset.

Keywords Unresectable pancreatic cancer · Chemotherapy · Gemcitabine · S-1 · Gemcitabine+S-1

Introduction

Pancreatic cancer (PC) currently is the fifth leading cause of cancer-related mortality in Japan, with an estimated 25,960 deaths attributable to the disease in 2010 [1]. Although surgical complete removal of the tumor is the only chance of cure, almost all PC patients are diagnosed at an advanced unresectable stage, despite recent improvements in diagnostic techniques. Moreover, since PC recurs in about 20% of patients even after surgical resection, development of effective chemotherapy is essential to improve the prognosis of this disease.

Gemcitabine (Gem) is widely used as a standard systemic chemotherapeutic agent for advanced PC [2]. Although some combination therapies including Gem have shown survival benefit, these are not considered as standard regimens [3, 4]. S-1 is a fourth generation oral fluoropyrimidine, which contains tegafur/gimeracil/oteracil potassium at a molar ratio of 1.0:0.4:1.0. The efficacy of S-1 has already been shown in a variety of solid tumors, particularly gastric cancer [5, 6]. A phase II trial of S-1 alone for PC metastatic to other organ has shown a response rate of 37.5% and a median survival of 9.2 months [7, 8]. Moreover, non-randomized phase II trials of a combination of Gem and S-1 (GS) therapy have demonstrated excellent results as to ORR of 44–48% and median survival of 10–12 months [9–13].

The current study (PC-01) was a randomized phase II trial to clarify the effectiveness of GS, prior to an anticipated phase III trial comparing GS with Gem alone, because there are many chemotherapy regimens that did not prove survival benefit despite the fact that one-arm phase II studies showed extremely promising results. Consequently, we, investigators of the Japan Clinical Cancer Research Organization (JACCRO), considered the current study (PC-01) could accurately elucidate the true activity of GS, because selection bias frequently seen in one-arm trials may be minimized by prospective randomization studies.

Patients and methods

Patients

The eligibility criteria for enrollment into this study (March 2007–August 2010) were patients with histologically or cytologically proven pancreatic adenocarcinoma, patients with International Union Against Cancer clinical stage III (locally advanced disease: T4N0-1 and M0) or IV (metastatic disease: T1-4N0-1 and M1), patients with measurable lesions as defined in the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 guidelines, age $\geq$20 and $\leq$80, no prior anticancer treatment for any malignancies, an Eastern Cooperative Oncology Group performance status (PS) $\leq$2, adequate bone marrow (leukocyte count $\geq$4,000/mm^3, neutrophil $\geq$2,000/mm^3, platelet count $\geq$100,000/mm^3, and hemoglobin $\geq$8.0 g/dl), adequate renal function (serum creatinine concentration $\leq$1.5 mg/dl and creatinine clearance $\geq$60 ml/min), adequate hepatic function (serum bilirubin level $\leq$2.0 mg/dl, serum alanine and aspartate transaminase levels $\leq$2.5 times the upper limit of the institutional normal; if biliary drainage was performed for jaundice before registration, the former $\leq$5 times the upper limit of the institutional normal and the

S. Ohoka
Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

Y. Hirose
Department of Surgery, Japanese Red Cross Fukui Hospital, 2-4-1 Tsukimi, Fukui-shi, Fukui 918-8501, Japan

N. Egawa
Department of Gastroenterology, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan

T. Ikari
Department of Internal Medicine, Tobu Chiiki Hospital Tokyo Metropolitan Health and Medical Treatment Corporation, 5-14-1 Kameari, Katsushika-ku, Tokyo 125-8512, Japan

T. Nakajima
Japan Clinical Cancer Research Organization, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan

latter ≤2.5 times the upper limit of the institutional normal), oxygen saturation ≥93%, adequate nourishment, no serious complications, life expectancy of at least 8 weeks, and provision of written informed consent from the patient.

Before randomization, a complete history was obtained and physical examination, routine hematology and biochemistry, ECG, chest X-ray, and abdominal computed tomography (CT) scan were performed.

Study design

PC-01 was an open-label, screening design, randomized phase II study. The primary end point was ORR. Secondary end points included treatment toxicity, clinical response benefit, PFS, and OS.

Patients were randomly assigned to the G group or the GS group in a 1:1 ratio. Random assignment was performed centrally by a web-based assistant system (flexible license assisted data server, JACCRO, Tokyo), using a computer-driven minimization procedure. Stratification factors were stage (III vs. IV), PS (0 or 1 vs. 2), and pain due to cancer (present vs. absent).

This study protocol was approved by the Protocol Review Committee of the JACCRO and Institutional Review Board of each institution, ClinicalTrials.gov identifier number was NCT00514163.

Protocol treatment

Eligible patients were randomly assigned to either the G group or the GS group. The G group patients received 1,000 mg/m^2 Gem intravenously during 30 min on days 1, 8, and 15, as 1 course repeated every 4 weeks. Patients with grade 4 hematological toxicities or grade 3 non-hematological toxicities underwent dose reduction to 800 mg/m^2 in the next course. The GS group patients received 1,000 mg/m^2 Gem intravenously during 30 min on days 1 and 8, and 40 mg/m^2 S-1 taken orally twice daily on days 1–14, every 3 weeks. When patients developed grade 4 hematological toxicities or grade 3 non-hematological toxicities by day 8, treatment was delayed by 1 week, and the S-1 dose was reduced to 60 mg/m^2 in the next course. In neither arms, prophylactic granulocyte-colony stimulating factor support allowed. Treatment was continued until progression, unacceptable toxicity, or patient refusal to continue the protocol treatment. The discontinuation of the protocol treatment for the reasons mentioned above was defined as protocol cessation.

Response and toxicity assessment

Toxicities were evaluated at each patient visit, according to the Common Terminology Criteria for Adverse Events version 3.0. CT or magnetic resonance imaging scans were performed at the baseline and after every 4 weeks to assess radiological response according to the RECIST version 1.0. Radiological tumor shrinkage of the primary tumor of the pancreas was assessed for all patients in the current study. ORR and DCR were set at the frequency of complete response plus partial response, in addition to stable disease among patients in each arm, respectively.

Clinical response benefit was assessed using daily analgesic consumption (measured in oral morphine-equivalent milligrams). Among patients who required opioid before the protocol treatment, patients whose opioid administration decreased to better than half of the baseline by day 1 of course 3 (8 weeks later in the G group and 6 weeks later in the GS group) were defined to be responders.

Statistical considerations

The primary endpoint was ORR. A sample size of 49 was required for a one-sided alpha value of 0.05 and a beta value of 0.20 with an expected response rate of 30% in the GS group and a threshold response rate of 10% in the G group. The protocol was activated in June 2007, and a total of 110 patients were planned for recruitment accounting for some drop-off

Table 1 Patient characteristics

Characteristics	G group (n = 59)	GS group (n = 53)	P value
	n	n	
Gender			
Male	35	32	1.00
Female	24	21	
Age			
<65	31	28	1.00
≥65	28	25	
ECOG PS			
0	45	44	0.66
1 or 2	14	9	
Locally advanced	18	13	0.53
Metastatic	41	40	
Metastatic sites			
Liver	30	28	0.85
Lymph node	10	6	0.43
Peritoneum	7	12	0.14
Lung	3	8	0.11
Ascites and/or pleural effusion			
Present	4	7	0.34
Absent	55	46	
Pain			
Present	20	17	1.00
Absent	39	36	

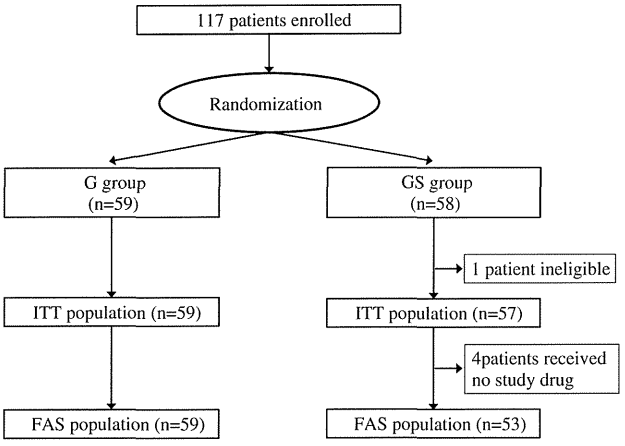

Fig. 1 Trial profile

cases within 1 year. If the null hypothesis (response rate) was not attained, the subsequent phase III trial would be designed to confirm the superiority of GS therapy to Gem alone.

The frequencies of each characteristic in Table 1 and each ORR and DCR in Table 3 were analyzed by the chi-square test.

OS was determined as the time from the date of registration to the date of death due to any cause and was censored at the date of the last follow-up for surviving patients. PFS was measured from the date of registration to the date of the first evidence of radiological or clinical progression, or death due to any cause and was censored at the date of the last follow-up CT for surviving patients with no clinical progression. OS and PFS were estimated by the Kaplan–Meier method, and the confidence interval (CI) was calculated with the Greenwood formula. Comparison of survival probability was conducted by the log-rank test. *P* values of less than 0.05 were considered to indicate statistically significant differences in the current study. The analysis was carried out with the SAS 9.2 statistical software (SAS Institute, Cary, NC, USA).

Results

Because of the poor recruitment rate, the protocol was amended twice, in January 2008 and February 2009, and a total of 117 patients were enrolled by August 2010 from 16 hospitals (see "Appendix"). One patient was judged to be ineligible after registration, because the final pathological diagnosis was not cancer. Accordingly, a total of 116 were allocated into either the G group ($N = 59$) or the GS group ($N = 57$) from among the intent-to-treat (ITT) population. Of the 116 patients, 4 in the GS group received supportive care instead of protocol treatment because of early deterioration or patient refusal. The full analysis set (FAS) consisted of 112, i.e., 59 and 53 patients in the G group and the GS group, respectively (Fig. 1).

Patient data registration was closed in June 2011, 10 months after the last patient registration. At the time of analysis, protocol treatment had been continued in 1 of 53 patients in the GS group. All analyses in comparison between the G group and the GS group were done in the FAS population, except OS.

Patient characteristics

Patient characteristics are shown in Table 1. The median age in the G group was 64 (41–79) years old, and that in the GS group was also 64 (45–77) years old. Although the protocol allowed enrollment of patients with PS 2, almost all patients were in good general condition (PS 0:1:2 was 79%:18%:3%, respectively). Metastatic disease was found in 72% of the patients. Analgesics (including opioids) were used in 33% (19%) of the patients at the baseline.

Toxicity

The major grade 3–4 adverse events are shown in Table 2. Although the frequency of grade 3–4 adverse events in the GS group was higher than that in the G group regarding both hematological and non-hematological toxicities, the toxicities were predictable and manageable. Discontinuation of the protocol treatment due to toxicity was seen in 13 (22%) of 59 protocol-cessation patients in the G group, and 14 (27%) of 52 protocol-cessation patients in the GS group. Treatment-related death was reported in 1 patient in each arm.

Clinical response benefit

At baseline, 12 and 10 patients required opioids in the G group and the GS group, respectively. There were 0 responders to opioids of 12 in the G group, and 2 of 10 in the GS group.

Objective response

Radiological responses are shown in Table 3. There was no complete response. The ORR in the GS group (28.3%) was significantly higher than that in the G group (6.8%), and the null hypothesis was rejected (two-sided $P = 0.005$). Also the DCR in the GS group was significantly higher.

In 31 patients with locally advanced disease, partial response was demonstrated in 1 (5.6%) of 18 patients in the G group, and 3 (23%) of 13 patients in the GS group. In the remaining 81 patients with metastatic disease, partial response was seen in 3 (7.3%) of 41 patients in the G group, and 12 (30%) of 40 patients in the GS group.

Table 2 Summary of maximum toxicity grades

Event	G group (n = 59)			GS group (n = 53)		
	Grade 3 (%)	Grade 4 (%)	Grade 3/4 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3/4 (%)
Hematological						
WBC	5.1	0	5.1	20.8	5.7	26.4
Hemoglobin	5.1	0	5.1	7.5	0	7.5
Neutrophil	20.3	1.7	22.0	41.5	13.2	54.7
Platelet	3.4	1.7	5.1	7.5	7.5	15.1
Non-hematological						
Fatigue	5.1	1.7	6.8	3.8	0	3.8
Anorexia	5.1	0	5.1	3.8	0	3.8
Nausea	1.7	0	1.7	3.8	0	3.8
Diarrhea	0	0	0	3.8	0	3.8
Stomatitis	0	0	0	3.8	0	3.8
Skin rash	0	0	0	7.5	1.9	9.4
AST	3.4	0	3.4	1.9	0	1.9
ALT	6.8	0	6.8	3.8	0	3.8
ALP	6.8	0	6.8	3.8	0	3.8
Bilirubin	6.8	0	6.8	1.9	0	1.9
Albumin	0	0	0	1.9	0	1.9
C-reactive protein	0	0	0	1.9	0	1.9
Treatment-related death	1.7			1.9		

Progression-free survival

PFS curves are shown in Fig. 2. Discontinuation of the protocol treatment due to progression was seen in 34 (58%) of 59 protocol-cessation patients in the G group, and 20 (38%) of 52 protocol-cessation patients in the GS group. The median progression survival time in the GS group (6.15 months) was significantly longer than that in the G group (3.78 months, $P = 0.0007$).

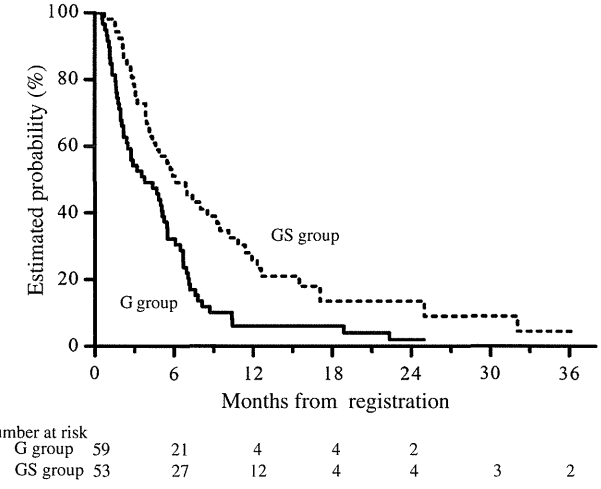

Fig. 2 Kaplan–Meier estimates of progression-free survival (n = 112)

Post-study treatment

After discontinuation of the protocol treatment, 37 (67%) of 55 patients in the G group and 23 (44%) of 52 patients in the GS group received various second-line treatments, most of which consisted of Gem or S-1 or both.

Overall survival in the ITT population

OS curves in the G group ($N = 59$) and the GS group ($N = 57$) are shown in Fig. 3. The GS group included 4 patients who deteriorated early or refused before protocol treatment, and subsequently received best supportive care without any anti-cancer treatment. The median survival time and 1-year survival probability in the G group and the GS group were 8.0 months and 29.0%, and 13.7 months and 55.9%, respectively. OS was significantly better in the GS group ($P = 0.035$), and its hazard ratio was 0.63 (95%, 0.41–0.97).

OS curves in the relation to extent of original disease are shown in Figs. 4 and 5. The median survival time in locally advanced and metastatic disease in the G group and the GS group were 8.7 and 7.7 months, and 14.6 and 12.9 months, respectively. OS in metastatic disease was significantly better in the GS group ($P = 0.029$).

Table 3 Objective response

Total (n = 112)	G group (n = 59)	GS group (n = 53)	P value
	n (%)	n (%)	
Complete response	0	0	–
Partial response	4 (6.8)	15 (28.3)	
Stable disease	22 (37.3)	19 (35.9)	
Progressive disease	23 (39.0)	7 (13.2)	
Not evaluable	10 (17.0)	12 (22.6)	
Objective response rate (%)	6.8	28.3	0.005
(95% CI)	(2.7–16.2)	(18.0–41.6)	
Disease control rate (%)	44.1	64.2	0.039
(95% CI)	(32.2–56.7)	(50.7–75.7)	

Locally advanced (n = 31)	G group (n = 18)	GS group (n = 13)	P value
	n (%)	n (%)	
Complete response	0	0	–
Partial response	1 (5.6)	3 (23.1)	
Stable disease	7 (38.9)	5 (38.5)	
Progressive disease	5 (27.8)	0	
Not evaluable	5 (27.8)	5 (38.5)	
Objective response rate (%)	5.6	23.1	0.284
(95% CI)	(1.0–25.8)	(8.2–50.3)	
Disease control rate (%)	44.4	61.5	0.473
(95% CI)	(24.6–66.3)	(35.5–82.3)	

Metastatic (n = 81)	G group (n = 41)	GS group (n = 40)	P value
	n (%)	n (%)	
Complete response	0	0	–
Partial response	3 (7.3)	12 (30.0)	
Stable disease	15 (36.6)	14 (35.0)	
Progressive disease	18 (43.9)	7 (17.5)	
Not evaluable	5 (12.2)	7 (17.5)	
Objective response rate (%)	7.3	30	0.011
(95% CI)	(2.5–19.4)	(18.1–45.4)	
Disease control rate (%)	43.9	65	0.075
(95% CI)	(29.9–59.0)	(49.5–77.9)	

Discussion

We set out to determine whether a combination of S-1 plus GS would obtain better results than GEM alone in a phase II study of unresectable pancreatic cancer.

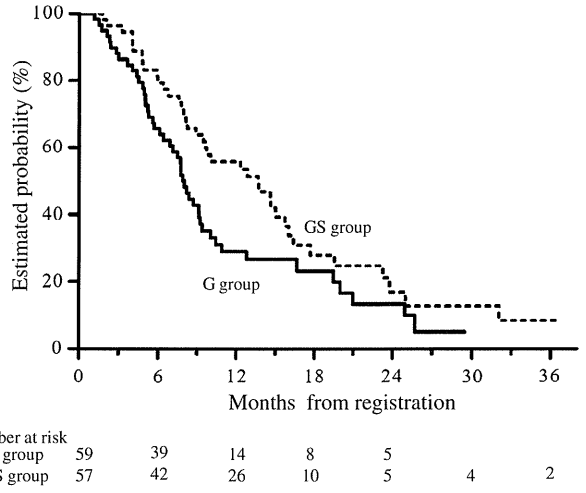

Fig. 3 Kaplan–Meier estimates of overall survival (n = 116)

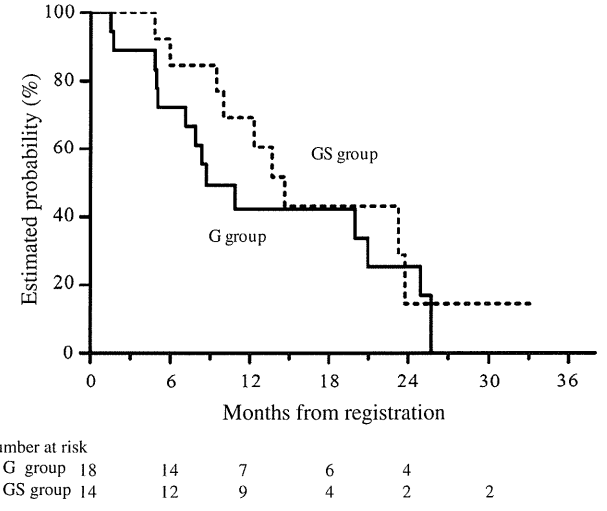

Fig. 4 Kaplan–Meier estimates of overall survival in locally advanced (n = 32)

The current PC-01 study, which was intended to screen GS as a promising investigation for a phase III trial comparing to standard Gem alone, successfully met this primary endpoint. Although the response rate obtained in the current study was lower than that in the previous one-arm phase II trials, the anticancer activity of GS was confirmed to be stronger than Gem alone [9–13]. Favorable results of GS as to PFS and OS data also encouraged us to plan a large phase III study comparing GS to standard Gem alone. However, results of large randomized phase III study of GS and Gem alone, known as the GEST trial, which was started by another Japanese cooperative group after our PC-01, were reported at the latest annual meeting of American Society of Clinical Oncology 2011 [14]. This large-scale (N = 600) GEST did not show OS superiority of GS compared to Gem alone. In terms of the survival benefit, this study seems to contradict the present PC-01 study.

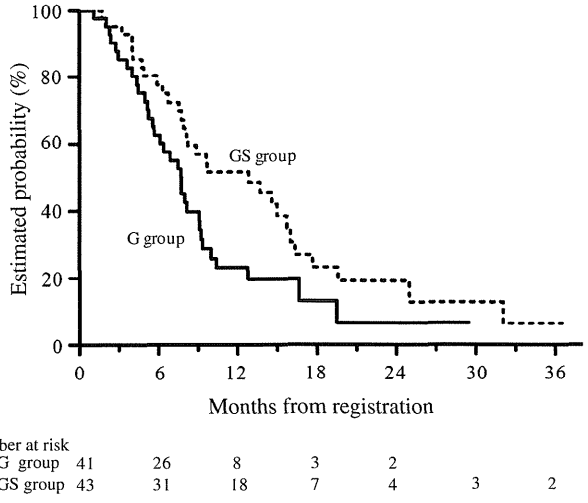

Fig. 5 Kaplan–Meier estimates of overall survival in Metastatic ($n = 84$)

Fluoropyrimidine and its derivatives have been intensively examined in combination with Gem for PC [15, 16]. All of those combinations have failed to show OS superiority compared to Gem alone in phase III settings, whereas relatively favorable results were generally reported in terms of response rate and survival. Accordingly, it may be important to explore a specific population in whom benefit would be maximized by GS therapy, though it may be difficult to develop Gem and fluoropyrimidine combination as a conventional frontline regimen for standard risk cases with advanced PC.

The main limitation of the PC-01 study derived from its inclusion of a relatively large number of patients who were found to be non-evaluable, mainly due to either the deterioration of the disease or patient refusal, which might well have affected the outcome of local response. On the other hand, randomized comparison of GS and Gem alone was one of the strengths of the current study. The ORR of GS in a previous non-randomized phase II study was extremely high, around 40%, perhaps due to selection bias [9–13]. However, in actual practice, since the response rate is usually below 30%, the PC-01 demonstrated a response rate acceptable to medical oncologists. Although PC-01 was not a phase III trial designed to confirm survival benefit, the OS and PFS data in the ITT population were impressive. The GS group showed a significant survival advantage against Gem group, even though the GS group included 3 cases of early deterioration. In the subset analysis, there was some discrepancy for the favorable population for GS between the current PC-01 and the GEST study. For example, GS was favorable in metastatic disease in PC-01; on the other hand, it was favorable in locally advanced disease in the GEST. GEMSAP, another Japanese study group, also carried out a randomized phase II trial of GEM and GS comparison and reported GS superiority to GEM in PFS in ASCO2011 [17].

Further accumulation of GEM and GS data might warrant an integrated meta-analysis to identify the population most likely to benefit from GS. Subsequently, a large randomized phase III trial to confirm GS advantages in a specific patients subset may be justified.

In conclusion, PC-01 demonstrated that GS had strong anticancer activity, and we believe that GS in some situations would be beneficial to give advanced PC patients.

Acknowledgments We are grateful to K. Aiba, Y. Shimada, and R. Kuwatsuru for their kind advice. We also thank T. Sudo and S. Koyama for their data management and Prof M. Takeuchi of Kitasato University for his rigorous statistical analysis. The authors are also indebted to Prof. J. Patrick Barron, Chairman of the Department of International Medical Communications of Tokyo Medical University, who is a remunerated consultant of Taiho Pharmacology for his review of this manuscript. This study was presented in part at the 2011 ASCO Annual Meeting, Chicago, Illinois and the 9th Annual Meeting of the Japanese Society of Medical Oncology, Yokohama, Japan, 2011. This study was supported by JACCRO.

Conflict of interest No authors have any conflict of interest.

Appendix

The following investigators registered patients for this study:

Hiroshi Ishii (Cancer Institute Hospital, Tokyo, Japan); Yuji Matsumura (Juntendo University School of Medicine, 2-1-1 Tokyo, Japan); Naoto Egawa, Yasushi Omuro (Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan); Atsushi Sofuni, Fumihide Itokawa (Tokyo Medical University Hospital, 6-7-1, Nishi-Shinjuku, Tokyo, Japan); Hisatsugu Mouri (Kanazawa University,13-1, Ishikawa, Japan); Keiji Hanada, Tomohiro Iiboshi (JA Onomichi General Hospital, Hiroshima, Japan); Yasutoshi Kimura (Sapporo Medical University School of Medicine, Hokkaido, Japan); Takeo Ukita, Takuro Endo, Hiroaki Shigoka (Toho University Ohashi Medical Center, Tokyo, Japan); Yusuke Ishida (Kurume University School of Medicine,Fukuoka, Japan); Manabu Kawai (Wakayama Medical University, Wakayama, Japan); Takaaki Ikeda (Yokosuka Kyosai Hospital, Kanagawa, Japan); Tsutomu Hijioka (Kumamoto Red Cross Hospital, Kumamoto, Japan); Ryohei Watanabe (Matsuyama Shimin Hospital, Ehime, Japan); Shinya Ohoka (Tokyo Medical and Dental University, Tokyo, Japan).

Yuki Hirose (Japan Red Cross Fukui Hospital, Fukui, Japan); Takaaki Ikari (Tobu Chiiki Hospital Tokyo Metropolitan Health and Medical Treatment Corporation, Tokyo, Japan).